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EXAMINER	
LAM, ANN Y	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/560,315	SPIRA ET AL.	
	Examiner	Art Unit	
	ANN Y. LAM	1641	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 September 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-43* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-7 and 10-43* is/are rejected.

7)☒ Claim(s) *8 and 9* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *2/17/09, 9/12/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-43 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1, recites in line 1 “A surface-substrate”, and in line 4 “the surface”. It is not clear as to what is meant by “surface-substrate”. (A combination of a surface and a substrate? Or a substrate having a surface?) Thus it is not clear whether "the surface" refers to the surface part of a combination or the surface of the substrate. Thus, Claims 2-43 are rejected because they depend from claim 1.

Claim 8 recites “wherein the hydrolytic enzyme is selected from polysaccharide, degrading enzymes, proteinases and lipid-degrading-enzymes.” However, claim 8 depends from claim 5, which recites such hydrolytic enzymes as an alternative. Thus, it is not clear whether or not claim 8 is reciting the hydrolytic enzymes as the moiety, rather than as one of 3 alternatives. For examination purposes, the hydrolytic enzyme is considered the moiety in claim 8. (Applicant can overcome this rejection by, for example, reciting in claim 8, -- wherein the internalization-promoting moieties are hydrolytic enzymes that facilitate degradation of extracellular matrix, and the hydrolytic enzyme is

selected from …….--) Claim 9 is rejected, since it depends from claim 8, which is vague as discussed above.

Claim 32, recites in line 2, “the receptor molecules”. The claim lacks antecedent basis for this limitation. For examination purposes, the term is interpreted to be referring to the “immobilized recognition molecules’ recited in claim 29, from which claim 32 depends.

Claim 29 recites “An electrode according to claim 24, coated with a layer of immobilized recognition molecules that, in the presence of cell-secreted components, catalyze a reaction that causes release of ions in a media surrounding said recognition molecule.” Claim 29 depends from claim 24, which depends from claim 17, which recites "A surface-substrate according to claim 1, adapted to form a cell-communicating part of an electrode." Claim 1, in turn recites “A surface-substrate for adherence of cells thereto comprising: at least one micronail structure protruding from the surface, at least a region of said micronail having cellular-internalization promoting properties.” Moreover, according to Applicant’s disclosure, the cellular internalization promoting properties are obtained by cellular internalizaton-promoting moieties coated on the micronail (see e.g. claim 2). However, claim 29, which depends from claim1, recites that the electrode, which comprises the surface-substrate of claim 1, is coated with a layer of immobilized recognition molecules that catalyze a reaction that causes release of ions. It is not clear whether or not the entire electrode or surface-substrate is coated with this recognition molecules, because such would be in contradiction to claim 1, which appear to imply (based on Applicant’s

disclosure) that the surface-substrate (electrode) is coated at least in a region with cellular internalization-promoting moieties. It appears that claim 29 intends to refer to a partial coating in another region of the electrode or surface-substrate with the recognition molecules that catalyze a reaction that causes release of ions. However this is not clear. Claims 30-40 are rejected since they depend from claim 29, which is unclear as discussed above.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-7, 10, 12, 13, 17-22, 24-28 and 41-43 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lu et al., WO 03/104789 A1, in view of Yitzchaik et al., WO00/51191.

Lu et al. disclose a biosensor having a substrate 16, a conductive thin film 14, a ZnO nanotip array 12 on the conductive film 14, and metal electrode pad 17. A reaction between the immobilized species on ZnO nanotips 12 with the target will result in the total change accumulated on the nanotips, and will cause a transient current across the biosensor device. Paragraph 0026.

The conductive thin film 14 has certain conductivity, and it can be a semiconductor, a metallic thin film, or a multilayer thin film. The thin film and the metal bond pads are deposited on the substrate 16, then patterned using the standard microelectronic processing techniques. Paragraph 0028.

The ZnO nanotips serve as DNA or protein molecule binding sites. The ZnO nanotips 12 are preferably bonded with protein or DNA molecules to make conductivity-based biosensors. Preferably a probe is attached to the tip to seek the targeted molecule due to bioreaction. The probe may preferably be attached on a binding site or a target molecule preferably has a probe. The dimensions of the conductive pattern, the aspect ratio and doping level of the ZnO nanotips, are optimized to enhance the sensitivity. Due to depletion or accumulation of carriers in the nanotips as a result of bioreactions, the conductance of the patterned tip arrays will change significantly. The depletion or accumulation of the nanotips will result in a transient current across the line. The amplitude of this current will be a functionof the amount of target material detected and the duration of the reaction time. Paragraph 0030.

The sharp ZnO nanotips 12 provide the favorable binding sites to enhance the immobilization, and increase the effective sensing area, and therefore improve the sensing and detection efficiency. The changes in electrical conductivity, and/or optical absorption, and/or fluorescence in conductive and semiconductive ZnO nanotips will be used to sense the targeted biochemcial reactions. Paragraph 0055. The ZnO biosensors are used to detect RNA-DNA, DNA-DNA, protein-protein, protein-DNA, and protein-small molecule interactions.

Optimum immobilization conditions can be used for the biosensors to further enhance their sensitivities and specify the target molecules. Paragraph 0056.

Thus, as to claim 1, the substrate 16 and conductive thin film 14 together are equivalent to Applicant's claimed surface-substrate, the nanotip(s) 12 are equivalent to the claimed micronails(s) protruding from the surface. The nanotips, having sharp tips and biological probes that for example provide for protein-protein interactions.

However, Lu et al. do not teach that the micronail structure has cellular-internalization promoting properties.

However Yitzchaik et al. disclose an electrical junction enabling the coupling between electrical devices and voltage sensitive cells (neurons, muscle cells and gland cells) for various utilities, such as a sensor to detect electrical activity in voltage sensitive cells (page 10, lines 16-21.) A single transistor can be used for stimulation and sensing, or two adjacent transistors can be utilized, one for stimulation and one for sensing (page 12, lines 8-11.)

It is further disclosed by Yitzchaik et al. that the anchoring of the voltage sensitive cells (VSC) to the external surface of the transistor can be achieved by a plurality of binding moieties such as antibodies, receptors, ligands, lectins and adhesion molecules. Where the VSC is a neuron, typically the binding molecules are adhesion molecules such as small molecular weight peptides derived from the neurite promoting domains of laminine (an extracellular matrix protein), (page 13, lines 4-9). Where the VSC is a neuron, the binding moieties may be used not only to anchor the VSC to the surface of the transistor, but also to direct the

growth of the neuron to the proper location in the transistor, and repulse its growth from an undesired location (page 13, lines 13-16.) The binding moieties are immobilized on the external surface of the transistor (page 15, lines 3-4.)

It is also taught by Yitzchaik et al. that preferably the transistor of the junction utilizes silicon-based integrated technology, but may alternatively utilize any other semiconductor structure (page 14, lines 3-5.) The invention provides an advanced MOS-FET structure using floating gate devices (page 14, lines 23-25.)

It would have been obvious to one of ordinary skill in the art at the time the invention was made to combine the teachings of Lu et al. and Yitzchaik et al. to provide binding moieties to anchor voltage sensitive cells to the Lu et al. nanotips in order to detect electrical activity in voltage sensitive cells as desirable to the skilled artisan for any of various known studies. Specifically, given the teachings of Lu et al. that binding moieties can be used to anchor biological materials, specifically biomolecules, to a conductivity-based biosensor comprising a transistor for detecting current changes, and given the teachings of Yitzchaik et al. that binding moieties can be used to anchor specifically biological cells to a sensor for detecting electrical activity in the cell, the sensor also comprising a transistor, the skilled artisan would have recognized that the Lu et al. invention can likewise be provided with a binding moiety that binds a cell to the transistor for detection of conductivity or electrical activity in the cell for study.

The binding moiety that anchors the cell to the nanotip of Lu et al. provides the nanotip with cellular-internalization promoting properties since, as

claimed and disclosed by Applicant, such cellular-internalization promoting properties can be provided by moieties that recognize plasma membrane components located on the external surface of the plasma membrane of cells. That is, mere binding of the cells appear to be convey cellular-internalization property on the nanotip.

As to claim 2, providing (coating) the moieties on the nanotip has been discussed above.

As to claim 3, the portion of the conductive thin film 14 (the portion of the thin film and portion of substrate 16) (figure 2, Lu et al.) immediately around the nanotip 12 is equivalent to the claimed base portion. (The remainder of the conductive thin film 14 and/or substrate is equivalent to the claimed surface substrate. The nanotip is equivalent to the claimed head portion having the cellular internalization promoting properties.

As to claim 4, providing cellular internalization-promoting moieties on the nanotips has been discussed above regarding claim 1.

As to claim 5, the internalization-promoting moieties are molecules that recognize plasma membrane components located on the external surface of the plasma membrane of cells, as discussed above regarding claim 1.

As to claim 6, the ZnO material on the nanotip (head portion) is composed of a metal containing material.

As to claim 7, the nanotip can be coated with gold (Au) (page 8, lines 16-17, Lu et al.)

As to claim 10, Yitzchaik et al. disclose use of antibodies, receptors, ligands, lectins and adhesion molecules to anchor the cells (page 13, lines 13-16).

As to claim 12, the molecules promote adhesion of cells (see page 13, lines 4-9, disclosing adhesion molecules for anchoring cells.)

As to claim 13, since Applicant has not defined any specifics regarding the base portion of the micronail, a lower portion of the Lu et al. nanotip which also has binding moieties is considered the base portion of the micronail.

As to claim 17, the nanotip forms a cell-communicating part of an electrode.

As to claims 18, 24, 25, 41, 42, Lu et al. disclose that another embodiment is a ZnO nanotip-gate field-effect-transistor (FET). FETS have been used for chemical sensors. In a FET, a voltage bias applied to the gate of a FET will modulate the current flowing between its source and drain. Paragraph 0032. An FET type of biosensor can be realized by depositing ZnO nanotips on the gate region of the FET. The surface charge changes occurring with the target on the ZnO nanotips will result in a potential difference between the gate and the substrate, and modulate the current flowing between the source and the drain. Paragraph 0033. More specifically, an FET sensor is composed of a ZnO nanotip gate and a ZnO FET. Referring to figure 2, there is disclosed a substrate 22, semiconductor ZnO thin layer as a channel 24, doped ZnO source and drain regions 25, a gate insulator 26, metal electrodes 27 to the source and drain

regions 25, the ZnO nanotips 12 deposited on the gate, and an encapsulation layer 28 to protect the device except the nanotip gate area. Paragraph 0034.

As to claim 19, the entire lower portion of 12 as well as conductive thinfilm 14 is considered a base portion of the micronail. Since the substrate can be an insulating substrate, such as glass or sapphire (paragraph 0027), the "base portion of the micronail" is electrically isolated from its surrounding (the substrate.)

As to claim 20, the nanotip 12 and thinfilm 14 are considered to form the micronail, and they are electrically isolated from its surrounding, the glass substrate (paragraph 0027).

As to claim 21, Yitzchaik et al. that preferably the transistor of the junction utilizes silicon-based integrated technology, but may alternatively utilize any other semiconductor structure (page 14, lines 3-5.) The skilled artisan would have recognized that the ZnO nanotip can be substituted with other materials, such as silicon taught by Yitzchaik et al. since it would achieve the same intended purpose.

As to claim 22, the Lu et al. device is an integrated structure. (As to the method of manufacturing, these limitations are examined as product-by-process limitaitons, and thus are met by the prior art since the product is disclosed by the prior art.)

As to claim 26, the Lu et al. device (comprising an lectrode) has at least a single micronail (see figure 1) (There is no limitation requiring only a single micronail, since the term "having" is equivalent to --comprising--.)

As to claim 27, a cluster of micronails is disclosed in figure 1 of Lu et al.

As to claim 28, Lu et al. do not disclose that the size of the cluster is smaller than the size of the cell. However, Lu et al. disclose that the dimensions of the conductive pattern, the aspect ratio and doping level of the ZnO nanotips, are optimized to enhance the sensitivity (paragraph 0030). Providing the size of the cluster in the relative dimension recited by Applicant appear to be within a workable or optimum range for enhancing sensitivity, and thus would have been within the skills of the ordinary artisan.

As to claim 43, the detecting of current changes in cells has been discussed above regarding claim 1.

Claim 11 is rejected under 35 U.S.C. 103(a) as being unpatentable over Lu et al., WO 03/104789 A1, in view of Yitzchaik et al., WO00/51191, and further in view of Witt et al., 5,795,860.

The teachings of Lu et al. and Yitzchaik et al. have been discussed above. However, neither Lu et al. nor Yitzchaik et al. specifically teach use of binding moieties that bind to polysaccharides that are part of the proteoglycans in the ECM plasma membrane.

However, it is noted that Yitzchaik et al. disclose in general, use of binding moieties such as antibodies, receptors, ligands, lectins and adhesion molecules

for anchoring the cells to the surface of the transistor (page 13, lines 4-9; and page 13, lines 4-9.) Thus, the skilled artisan is suggested to use known moieties that bind to cell surfaces, and would look to the art, such as the Witt et al., for such binding moieties.

Witt et al. teach glycan-binding proteins that bind with specific, determinable oligodisaccharide structures (glycans) pendant from proteoglycans immobilized on a cell, and which have relatively high affinity and specificity for a given glycan-binding protein (col. 7, line 66 to col. 8, line 19.) The skilled artisan would have recognized that such glycan-binding proteins can be used as the specific binding moieties suggested by Yitzchaik et al. for binding and thus anchoring cells.

Claims 14 and 15 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lu et al., WO 03/104789 A1, in view of Yitzchaik et al., WO00/51191, and further in view of Meyers et al., 4,546,083.

The teachings of Lu et al. and Yitzchaik et al. have been discussed above. While Yitzchaik et al. disclose in general, use of binding moieties such as antibodies, receptors, ligands, lectins and adhesion molecules for anchoring the cells to the surface of the transistor (page 13, lines 4-9; and page 13, lines 4-9),

there is no specific disclosure of a monolayer of polylysine. However, the skilled artisan is suggested by Yitzchaik et al. to use known cell anchoring compounds, such as polylysine as disclosed by Meyers et al. (see claim 8 in Meyers et al.), as the specific type of adhesion molecules for anchoring cells, and thus such use would have been obvious.

Claim 16 is rejected under 35 U.S.C. 103(a) as being unpatentable over Lu et al., WO 03/104789 A1, in view of Yitzchaik et al., WO00/51191, and Meyers et al., 4,546,083, as applied to claim 15 above, and further in view of Singh et al., 7,270,973.

The teachings of Lu et al. and Yitzchaik et al. and Meyers et al. have been discussed above. However, neither Lu et al. nor Yitzchaik et al. nor Meyers et al. teach that the polysilane (taught by Meyers et al.) is assembled on a polystyrenesulfonate layer comprising anion units connected through a linker to the micronail.

However Singh et al. teach that multilayers can be fabricated on materials that are normally thought of as inert, provided that their surface is first chemically modified to generate functional groups that can support subsequent adsorption of the charged polymers or enzymes. For example, films of polytetrafluoroethylene (PTFE) or Teflon.RTM. are normally non-adhesive materials; i.e, it is difficult to adsorb other materials to these films. However,

brief oxidation of the surface using a plasma creates highly acidic surface hydroxyl groups, which readily deprotonate to form anionic functional groups on the surface. Aminosiloxane self-assembled monolayers can be chemisorbed to these species, providing a reactive amine terminated monolayer coating on the PTFE or Teflon.RTM. film. These reactive amines can be used to bind other materials, such as metals, with good adhesion to the underlying PTFE or Teflon.RTM. Because the surface hydroxyl groups present on plasma oxidized films of PTFE or Teflon.RTM. deprotonate in water to form surface anions, adsorption of a cationic polyelectrolyte such as the branched polyethylenimine (BPEI), which is used as the first layer of the multilayer films, on these surfaces is possible. In addition, the possibility also exists to use a PTFE or Teflon.RTM. film bearing a chemisorbed aminosiloxane film as a base positively charged film in the multilayer assemblies described below. Such an aminosiloxane film might be used to directly bind an enzyme layer during the fabrication of a multilayer film. Alternatively, an aminosiloxane film might be used to bind a layer of anionic polyelectrolytes, such as polystyrenesulfonate (PSS), which could then serve as a base layer for binding the first layer of BPEI. Column 3, line 63 to col. 4, line 29.

Thus, Singh et al. teach use of polystyrenesulfonate layer in a multilayer film which can support adsorption of charged polymers or enzymes. Moreover, while the scope of the Singh et al. invention relates to catalytic enzyme-modified textiles, and, more specifically, to catalytic enzyme-modified textiles for active protection from air or water borne toxins by active passivation and adsorption of

toxic materials (col. 1, lines 13-18), the invention nevertheless utilizes binding technology to immobilize biochemicals (see e.g., col. 1, line 53 to col. 2, line 12.) Thus, use of such binding technology in the Lu et al.-Yitzchaik et al.-Meyers et al. invention would have been obvious to the skilled artisan, as the skilled artisan would look to the art for known binding techniques to anchor the cells.

Claim 23 is rejected under 35 U.S.C. 103(a) as being unpatentable over Lu et al., WO 03/104789 A1, in view of Yitzchaik et al., WO00/51191, as applied to claim 19, and further in view of O'Connor et al., US 20020009810A1, and Keeth et al., 6,465,331.

The teachings of Lu et al. and Yitzchaik et al. have been discussed above. However, neither Lu et al. nor Yitzchaik et al. disclose that a nanotip made of tungsten.

However, O'Connor et al. disclose a biosensor to detect molecular binding, using electrodes for detection of a change in impedance (paragraphs 0019 and 0020). Moreover, it is disclosed that the binding ligand is covalently attached to the electrode, and that the electrode can be made of a conductive or semi-conductive composition, which, when connected to an electronic control and detection device, is able to transmit electrons, and that preferred electrodes are known in the art and include, but are not limited to, certain metals and their

oxides, including gold; platinum; palladium; silicon; silicon oxide, tungsten oxide. Preferred electrodes include gold, silicon, carbon and metal oxide electrodes. Paragraph 0049.

Thus, it would have been obvious to one of ordinary skill in the art at the time the invention was made to utilize tungsten oxide as the conductive material in place of the zinc oxide (ZnO semiconducting material, paragraph 0022) disclosed by Lu et al. since the skilled artisan would have recognized that other materials would also serve the same intended purpose of electrical detection, as shown by O'Connor in teaching that an electrode for impedance detection can be of a conductive or semi-conductive composition.

Also, neither Lu et al., Yitzchaik et al., nor O'Connor et al. teach that the nanotip is isolated from the surrounding by a layer of silicon nitrade. However, the skilled artisan would have recognized that the Lu et al. substrate can be made of any various appropriate material, as it is disclosed by Lu et al. to be a semiconductor substrate, or glass or sapphire as examples (paragraph 0027).

Moreover, Keeth et al. disclose silicon nitrade as a spacer film that overlays a substrate that is etched back and planarized with the top of a gate stack. The spacer film isolates the gate stack from materials which are used in self-aligned contact etching. A think protective insulating layer may be formed on top of the gate stackes and over the substrate. Column 4, lines 21-3. Use of such known materials for producing a substrate, as taught by Keeth et al., to form the Lu et al. substrate would have been obvious to the skilled artisan since the skilled artisan would look to known methods of manufacturing, e.g., use of

silicon nitrade and etching disclosed by Keeth et al., to produce the Lu et al. substrate.

Claims 29-35, 37-40 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lu et al., WO 03/104789 A1, in view of Yitzchaik et al., WO00/51191, and further in view of Blackburn et al., 6,846,654.

The teachings of Lu et al. and Yitzchaik et al. have been discussed above. However, neither Lu et al. nor Yitzchaik et al. teach that the immobilized probes (recognition moiety), in the presence of cell-secreted components, catalyze a reaction that causes release of ion in a media surrounding the immobilized probes (claims 29 and 30), or that the such immobilized probes are enzymes (claim 32, or that such immobilized probes catalyze the reaction that release ions in the presence of a cell—secreted component that is acetylcholine or neurotransmitter (claim 33), or that the immobilized probe is acetylcholine esterase (claim 34), or that the gate-electrode is an ion sensitive gate (claim 35.)

However, such enzyme assays using electrode biosensors are known in the art as shown by Blackburn et al. It is disclosed by Blackburn et al. that a pH-based catalytic antibody biosensor incorporating antibodies which mimic choline ester receptor proteins, such as MOPC167, is used to detect chemical and biological warfare (CBW) agents and other inhibitors. For example, acetylcholine (Ach) is an important neurotransmitter which is stored in vesicles

in the synaptic terminals of cholinergic neurons and is released by neural impulses. The released neurotransmitter diffuses across the synaptic cleft and binds to Ach receptors in the post-synaptic neural membranes where the binding event stimulates a neural impulse. Many CBW agents act by binding to the Ach receptors and blocking the transmittance of neural impulses across the neural synapse. The catalytic antibody MOPC167 binds choline esters (mimicking the neural Ach receptors) and catalyzes their hydrolysis. As a specific example, MOPC167 catalyzes the hydrolysis of p-nitrophenyl N-trimethyl ammonioethyl carbonate (NTAC). The hydrolysis of choline esters, catalyzed by MOPC167, produces hydrogen ions which can be detected using a pH-based biosensor. Thus, Ach inhibitors are detected by sensing the change in hydrogen ion concentration resulting from catalysis inhibition. Column 37, lines 10-32.

In short, Blackburn et al.teach that recognition molecules (e.g., antibody) can be immobilized and used to bind to choline esters (acetylcholine)and catalyze their hydrolysis, which produces hydrogen ions, which can be detected using a pH-based biosensor.

Moreover, Blackburn et al. disclose that electrode biosensors for such detection are known in the art (col. 12,line 48 – col. 14, line 9). In particular, Blackburn et al. also disclose that one example of an immunochemical electrode is the immunochemically sensitive field effect transistor (IMFET). This detection scheme relies on the ability of a field effect transistor to measure changes in the interfacial charge at the membrane-solution interface, thus allowing

measurement of ionically charged antigen or antibody binding at the interface. Column 14, lines 3-9.

Thus, in sum, Blackburn et al. teach the desirability of performing assays using immobilized recognition molecules (e.g., antibody) that catalyze a reaction (hydrolysis) which produce hydrogen ions for detection in order to detect inhibitors of Ach neurotransmitter (the inhibitors being a toxin). Moreover, the use of the Lu et al. field effect transistor to detection the hydrogen ions produced in the above assay reaction would have been obvious to the skilled artisan, as shown by Blackburn et al. in disclosing immunochemically sensitive field effect transistors are an example of such detectors that allow measurement of charge change.

As to claim 30, Lu et al. teach that the device is a gate electrode (paragraph 0032, disclosing that the ZnO nanotip-gate field-effect-transistor (FET) and that FETS have been used for chemical sensors.)

As to claim 31, the above references do not disclose that the distance between the recognition molecules and the surface of the coated gate is smaller than 15Å However, use of known immobilization techniques encompass any of numerous surface chemistries (see e.g., pargraph 0061 of Lu et al.), and thus encompass spacing the recognition moieties from various distances from the surface of the gate. The distance recited by Applicant appear to fall within a workable range.

As to claims 37 and 38, linker molecules for covalent attachment are disclosed by Lu et al. (paragraph 0061.)

As to claim 40, Lu et al. teach that the device is a ZnO nanotip-gate field-effect-transistor (FET) and that FETS have been used for chemical sensor. Paragraph 0032. An FET type of biosensor can be realized by depositing ZnO nanotips on the gate region of the FET. The surface charge changes occurring with the target on the ZnO nanotips will result in a potential difference between the gate and the substrate, and modulate the current flowing between the source and the drain. Paragraph 0033.

Claim 36 is rejected under 35 U.S.C. 103(a) as being unpatentable over Lu et al., WO 03/104789 A1, in view of Yitzchaik et al., WO00/51191, and Blackburn et al., 6,846,654, as applied to claim 35 above, and further in view of O'Connor et al., US 20020009810A1.

The teachings of Lu et al., Yitzchaik et al. and Blackburn et al. have been discussed above. However, these references do not disclose a nanotip made of silicon oxide.

However, O'Connor et al. disclose a biosensor to detect molecular binding, using electrodes for detection of a change in impedance (paragraphs 0019 and 0020). Moreover, it is disclosed that the binding ligand is covalently attached to the electrode, and that the electrode can be made of a conductive or semi-conductive composition, which, when connected to an electronic control

and detection device, is able to transmit electrons, and that preferred electrodes are known in the art and include, but are not limited to, certain metals and their oxides, including gold; platinum; palladium; silicon; silicon oxide, tungsten oxide. Preferred electrodes include gold, silicon, carbon and metal oxide electrodes. Paragraph 0049.

Thus, it would have been obvious to one of ordinary skill in the art at the time the invention was made to utilize silicon oxide as the conductive material in place of the zinc oxide (ZnO semiconducting material, paragraph 0022) disclosed by Lu et al. since the skilled artisan would have recognized that other materials would also serve the same intended purpose of electrical detection, as shown by O'Connor in teaching that an electrode for impedance detection can be of a conductive or semi-conductive composition.

Allowable Subject Matter

Claims 8 and 9 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to ANN Y. LAM whose telephone number is (571)272-0822. The examiner can normally be reached on Mon.-Fri. 10-6:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Mark Shibuya can be reached on 571-272-0806. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Ann Y. Lam/
Primary Examiner, Art Unit 1641